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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/582,826	06/14/2006	Kenneth L. Arrington	21596P	8251

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EXAMINER	
RAO, DEEPAK R	
ART UNIT	PAPER NUMBER
1624	
MAIL DATE	DELIVERY MODE
03/06/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/582,826	ARRINGTON ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,20-23 and 27-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,20-23 and 27-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20070220*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-7, 9, 20-23 and 27-33 are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7, 9, 20-23 and 27-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating ovarian carcinoma, does not reasonably provide enablement for a method of treating all other types of cancer; or a method of preventing cancer; a method of treating all types of cancer in combination with radiation therapy; a method of treating or preventing cancer in combination an additional compound (as recited in claims 21, 23, 27-31); a method of modulating mitotic spindle formation; or a method of inhibiting the mitotic kinesin KSP. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the

claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant claim 7, 9, 20-23 and 27-33 are drawn to – 'a method of treating or preventing cancer'; 'a method of modulating mitotic spindle formation'; and 'a method inhibiting the mitotic kinesin KSP'- all of which appear to be reach through claims. Reach through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through any or all diseases, disorders or conditions for which they lack written description and enabling disclosure in the specification. In the instant case, because of the KSP inhibitory action of the compounds, it is recited that instant compounds are useful for treating all types of cancer for which there is no adequate written description and enabling disclosure in the instant specification.

The testing assays provided in the specification at pages 34-37, are related to KSP inhibition in standard enzyme assays (as disclosed in WO 01/30768). Based on the inhibition activity, the specification provides that the compounds are useful as 'modulators' of mitotic spindle formation or inhibitors of mitotic kinesin KSP, and therefore useful in the treatment of a variety of diseases, including all types of cancer. The term "modulating" generally encompasses blocking, activating, partial blocking and partial activating. However, the compounds were not shown to have all these properties. For example, it is revolutionary for a compound to be effective as a blocker, activator and partial blocker/activator. The specification did not provide any competent tests or data to establish that the compounds have 'mitotic spindle formation modulating activity'. Next, applicant did not state on record or provide any guidance that the assay provided is correlated to the clinical efficacy of the treatment of various disorders of the

claims. As can be seen from specification, the activity data holds significant role in determining the dosage regimen based on the minimal effective concentration of each of the compound to achieve the desired inhibition of mitotic kinesin, or specifically KSP.

Farrell et al. (PubMed Abstract enclosed) provide that "Although recent structural, biochemical, and mechanical measurements are beginning to converge into a common view of how kinesin converts the energy from ATP turnover into motion, it remains difficult to dissect experimentally the intermolecular domain cooperativity required for kinesin processivity" (see the abstract). Another state of the art reference, Yildiz et al. (Trends in Cell Biology 2005) provides that "Kinesins are microtubule-based motor proteins that are involved in cargo transport and mitosis. … However, the mechanism underlying their motion has been unclear" (page 112). The reference concludes that "Clinical applications, however, require a deeper understanding of the mechanism and regulation of the motor proteins" (see page 119). This establishes the uncertainties and the level of unpredictability in the relevant state of the art and therefore, one of ordinary skill in the art would be required to go through undue experimentation to find the modulating activity of the compounds.

The scope of the claims includes any or all types of **cancer**, including those yet to be discovered for which there is no enabling disclosure. The scope of the claims is not adequately enabled solely based on the activity of the compounds provided in the specification at pages 34-37. The instant compounds are disclosed to have KSP inhibitory activity and it is recited that the instant compounds are therefore useful in treating any or all cancers stated in pages 18-19 for which applicants provide no competent evidence. For example, pages 18-19 include various cancers such as solid tumors such as skin, breast, brain, cervical carcinomas, testicular

carcinomas, etc. More specifically, Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma lymphoma, leiomyosarcoma), pancreas: (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangoma, Lipoma neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocacinoma choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma hepatoblastoma angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic,sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous hïstiocytoma, chondrosarcoma Ewing's sarcoma malignant lymphoma (reticulum cell sarcoma), multiple mycloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondoma, chondroblastoma chondrommyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma glioma,

ependymoma. germinoma (pinealoma), glioblastoma multiform, oligodendroglioma schwannoma, retinoblastoma, congenital humors), spinal cord neurofibroma meningioma glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. It appears that the applicants are asserting that the embraced compounds because of their mode action as KSP inhibitor that would be useful for all sorts of cancers. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most of cancers, such as colon, pancreatic and brain cancers are very difficult to treat and despite the fact that there are many anti cancer compounds including Taxol.

The instant claims include 'a method for the treatment of cancer' and the terms 'cancer' and 'proliferative disorders' represent anything that is caused by abnormal tissue growth. That

can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, polyps, etc. No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. The state of the art is not indicative any pharmaceutical agents that are useful in the treatment of cancer generally. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally.

The instant claims cover "a method of treating or **preventing** cancers" that are known to exist and those that are yet to be discovered and therefore, the use of the term is extremely broad. Further, there is no description regarding how to identify the subject 'in need of such treatment' in the disclosure. Test procedures for measuring the inhibition of KSP activity of the compounds is provided on pages 34-37, which involves microtubules of bovine brain, however, there is nothing in the disclosure regarding how the provided *in vitro* assay correlates to the treatment of

all types of cancers of the instant claims. The data provided in insufficient such that no reasonable extrapolation could be made by one skilled in the art regarding the activity of the compounds. The area of receptor interactions is highly structure specific and unpredictable. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area, and the inhibitory data provided is insufficient for one of ordinary skill in the art in order to extrapolate to treating and preventing all types of cancers. It is inconceivable as to how the claimed compounds are used, not only to treat but also to prevent the extremely difficult diseases embraced by the instant claims.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The instant claims 21-23 are drawn to 'a method of treating or preventing cancer that comprises administering a therapeutically effective amount of a compound of claim 1 in combination with an additional compound' and list numerous therapeutic agents. The

specification at pages 23-24 provides some examples of the additional agents intended by the claims, however, the scope of the claim includes agents that are known and those that may be discovered in future, for which there is no enablement. Further, the entire scope of the therapeutic activity intended for the compounds of the invention is not enabled for the reasons provided below.

The instant claims are drawn to 'A method of treating or **preventing** cancer', and therefore, the instant claim language embraces disorders not only for the treatment, but also for "prevention" which is not remotely enabled. Based on the KSP inhibitory activity of the compounds, the instant compounds are disclosed to be useful, not only in treatment but also in "prevention" of various types of cancers or diseases associated with the growth of cancerous tumor cells, for which applicants provide no competent evidence. "To prevent" actually means *to anticipate* or *counter in advance, to keep from happening etc.* (as per Websters II Dictionary) and therefore it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" effect. It is inconceivable based on the *in vitro* data provided in the specification, as to how the claimed compounds can, not only treat but also "prevent" the diseases of the instant claims. Further, there is no evidence on record which demonstrates that the *in-vitro* screening test relied upon is recognized in the art as being reasonably predictive of success in any of the contemplated areas of 'prevention'. Such a reasonable correlation is necessary to demonstrate such utilities. See *Ex parte Stevens*, 16 USPQ 2d 1379 (BPAI 1990); *Ex parte Busse et al.*, 1 USPQ 2d 1908 (BPAI 1986) (the evidence must be accepted as "showing" such utility, and not "warranting further study"). Furthermore, there is no evidence of record, which

would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disorders encompassed by the instant claims.

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

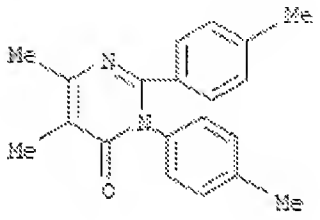
Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

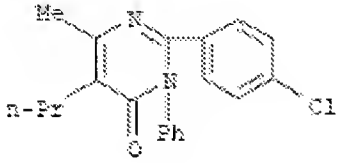
Claim Rejections - 35 USC § 102

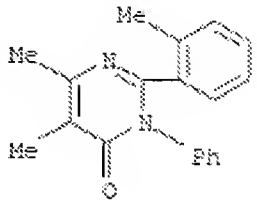
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

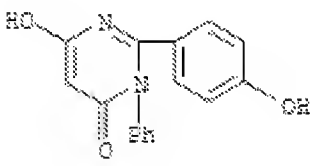
1. Claims 1 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Staskun et al., CAPLUS Abstract 51:39274 (1957). The instant claims read on reference disclosed compounds, see for example, the compounds in the enclosed copy of CAPLUS computer search report (representative structures of some of the disclosed compounds depicted below for convenience):

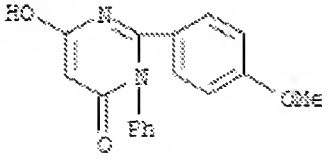


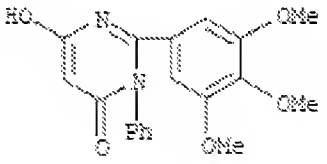




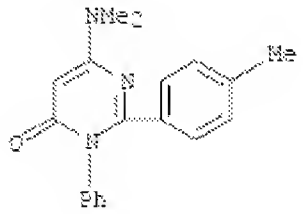
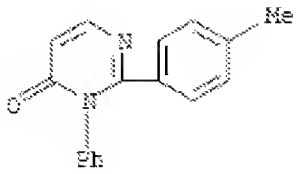
2. Claims 1 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Shchavlinskii et al., CAPLUS Abstract 88:50401 (1978). The instant claims read on reference disclosed compounds, see for example, the compounds in the enclosed copy of CAPLUS computer search report (structures of the disclosed compounds depicted below for convenience):





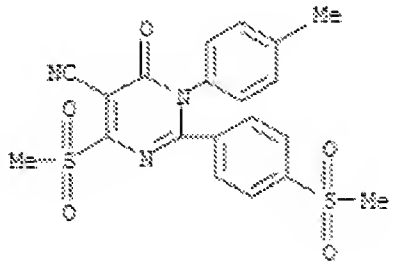


3. Claims 1 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Arai et al., CAPLUS Abstract 136:340653 (2002). The instant claims read on reference disclosed compounds, see the compound in the enclosed copy of CAPLUS computer search report (structure of the disclosed compound depicted below for convenience):

4. Claims 1, 5, 7, 9, 20-23 and 27-33 are rejected under 35 U.S.C. 102(b) and/or 102(e) as being anticipated by Agarwal et al., WO 03/084938 (published October 16, 2003; International filing date: April 10, 2003). The instant claims read on reference disclosed compounds, see the structural formula (I) in page 9 and the corresponding species in pages 13-14, see for example, the following compound:

5-Cyano-1-(4-methylphenyl)-4-methylsulfonyl-2-(4-methylsulfonyl-phenyl)-1,6-dihydro-pyrimidin-6-one;



The reference compounds are disclosed to be useful as pharmaceutical agents, for the treatment of conditions including cancer, see page 1. The instant claims 7, 9, 20-23 and 27-33 recite administering the compounds to the same patient population.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7, 9, 20-23 and 27-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agarwal et al., WO 03/084938. The reference teaches a generic group of pyrimidin-4-one compounds, which embraces applicant's instantly claimed compounds. See formula (I) in page 9, and the corresponding species in pages 13-14. The compounds are taught to be useful as pharmaceutical agents, see the discussion on page 1. Claims 1, 5, 7, 9, 20-23 and 27-33 are anticipated by the reference as rejected above under 35 U.S.C. 102. The remaining claims 2-4 and 6 differ from the reference by reciting specific species or a more limited subgenus than the reference. It would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the species of the genus taught by the reference, including those instantly claimed, because the skilled chemist would have the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole i.e., as therapeutic agents. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such

compounds would have been suggested by the reference as a whole. It has been held that a prior art disclosed genus of useful compounds is sufficient to render prima facie obvious a species falling within a genus. *In re Susi*, 440 F.2d 442, 169 USPQ 423, 425 (CCPA 1971), followed by the Federal Circuit in *Merck & Co. v. Biocraft Laboratories*, 847 F.2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir. 1989).

Receipt is acknowledged of the Information Disclosure Statement filed on February 20, 2007 and a copy is enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Monday-Friday from 8:00am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Deepak Rao/
Primary Examiner
Art Unit 1624

March 5, 2009